

## **REMARKS**

Claims 43 to 59 are pending. Claims 43 and 45 have been amended to more particularly point out and distinctly claim that which Applicants regard as the invention. In particular, claims 43 and 45 have been amended without prejudice, to recite, in part, methods for preventing development of a melanocyte to primary melanoma and/or treating metastatic melanoma. Applicants reserve the rights to prosecute the subject matter in one or more related applications. Support for these amendments can be found, *inter alia*, at page 15, lines 19-21, page 20, lines 5-18 and pages 24 to 26. Claim 43 has also been amended without prejudice, to recite, in part, that the method does not include antisense therapy. Support for the proposition that claims can be properly amended or drafted to exclude a particular species of a genus can be found in *In re Johnson*, 194 U.S.P.Q. 187 (C.C.P.A. 1977). Accordingly, the amendments are fully supported by the specification and do not introduce any new matter. Applicants respectfully request entry of the remarks made herein into the file history of the present application.

### **I. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN**

The Examiner has rejected claim 43 under 35 U.S.C. § 112, first paragraph for lack of enablement. In particular, the Examiner alleges that while the specification is enabling for the selective antagonism of the ETB receptor in a patient having melanoma comprising the administration of known peptide and antibody antagonists, the instant specification does not reasonably provide enablement for selectively antagonizing the ETB receptor by means involving the administration of antisense nucleic acid targeting endothelin B.

Although Applicants do not agree with the Examiner, in order to expedite prosecution, claim 43 has been amended to recite a method, in part, with a proviso to exclude antisense therapy.

For the foregoing reasons, Applicants respectfully request that the claim rejection under Section §112, first paragraph, be withdrawn.

### **II. THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN**

#### **1. The Pending Claims Are Not Obvious over Kikuchi**

Claims 43-46, 48, 50, 53, and 56-59 are rejected under 35 U.S.C. § 103(a) as obvious over Kikuchi et al., 1996, Biochem. Biophys. Res. Comm. 219:734-739 ("Kikuchi").

The Examiner alleges that Kikuchi provides the motivation for a person having ordinary skill in the art at the time the invention was made to administer BQ-788 to a patient having primary melanoma or a recurrent melanoma expressing the ETB receptor. Although Applicants do not agree with the Examiner, in order to expedite prosecution, Applicants have amended claims 43 and 45 to recite methods of preventing development of a melanocyte to primary melanoma and/or treating metastatic melanoma comprising selectively antagonizing the ETB receptor or administering a therapeutically effective amount of selective endothelin B receptor antagonist to a patient in need thereof. Applicants submit that Kikuchi fails to satisfy any requirements for establishing obviousness for the reasons discussed below and respectfully request that the rejection of claims 43-46, 48, 50, 53, and 56-59 be withdrawn on that basis.

In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q. 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 U.S.P.Q.2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 U.S.P.Q. at 467. These principles are reiterated in the "Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*" 72 Fed. Reg. 57526-57535 (2007) ("Guidelines").

The *KSR* Court rejected a rigid application of the "teaching, suggestion, or motivation" test previously applied by the Court of Appeals for the Federal Circuit. *KSR*, 127 S. Ct. at 1739 USPQ2d at 1395). However, the Supreme Court affirmed that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, S.Ct. at 1741, 82 USPQ2d at 1396. Both the suggestion and the reasonable expectation of success must be found in the prior art and *not* be based on the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 U.S.P.Q.2d (Fed. Cir. 1988).

With regard to the final point, the *KSR* Court citing *Graham*, upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue*. 127 S.Ct. at 1742, 82 U.S.P.Q. at 1397:

A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a “temptation to read into the prior art the teachings of the invention in issue” and instructing courts to “guard against slipping into the use of hindsight” (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))).

Thus, the principles set forth in *Graham* and in *Dow Chemical* -- which are still good law post-*KSR* -- require that *both* the suggestion and the expectation of success must be found in the prior art, and not derived from knowledge gained from the applicant’s disclosure.

Based on Kikuchi, one skilled in the art would conclude that an ETB-selective receptor antagonist, BQ-788, exhibited negative properties that are not suitable for the treatment of metastatic melanoma. In *Takeda Chemical Ind., Ltd. v. Alphapharm Pty., Ltd.*, 429 F.3d 1350 (Fed. Cir. 2007), the Federal Circuit held that the claims of a patent were not obvious when the closest prior art “exhibited negative properties that would have directed one of ordinary skill in the art away from that compound.” *Id.* at 1359. Here, Kikuchi’s teachings would have directed one of skill in the art away from the presently claimed methods. First, Kikuchi showed that the ETB receptor is down-regulated in metastatic melanoma cell lines (Kikuchi, Table 1 on page 736). Since Kikuchi reports that there are fewer ETB receptors in metastatic melanoma cells when compared to primary melanoma cells, one skilled in the art would conclude that Kikuchi teaches away from using an ETB-selective receptor antagonist for treating metastatic melanoma. Second, Kikuchi showed that there is a reduced growth response of metastatic melanoma cells induced by ET-1 and ET-3 compared to primary melanoma cell lines (Kikuchi, Fig. 2 and Table 2 on page 737, see cell lines PM-WK, RPM-EP and RPM-MC vs. MM-AN, MM-BP, MM-LH and MM-RU). This would further confirm for the skilled artisan that in metastatic melanoma cells, ETB receptors are down regulated.

Based on these teachings, one skilled in the art would not recognize that BQ-788 would have an effect on the transformation of a melanocyte into a melanoma or have an effect on metastatic melanoma. In fact, in Kikuchi, no experiments were performed to test the effect of BQ-788 on metastatic melanoma cells because the authors find no reason to do so.

Like the authors in Kikuchi, one skilled in the art, upon reviewing these teachings presented in Kikuchi, would conclude that BQ-788 would have no effect on metastatic melanoma cells. Not only does Kikuchi not suggest that BQ-788 would be used for the treating metastatic melanoma, in fact, Kikuchi teaches away from the present invention. Thus, one skilled in the art after reading Kikuchi would draw the same conclusion as the authors and would deduce that BQ-788 would have no effect on metastatic melanoma. It would have been counterintuitive for the skilled artisan to administer BQ-788 for treatment of metastatic melanoma. Accordingly, Kikuchi does not render the present invention obvious.

As admitted by the Examiner, decreasing tumor burden of the primary tumor, or causing disease stabilization of the primary tumor, and/or decreasing invasiveness of the primary tumor, is separate from inhibiting metastatic lesions (pages 5 and 6 of the final Office Action). Kikuchi is silent as to any effect of BQ-788 in the growth of metastatic melanoma. The only conclusion that Kikuchi draws regarding metastatic melanoma is that there are fewer ETB receptors in metastatic melanoma and that the reduced growth response of metastatic melanoma cells to ET-1 and ET-3 is due to the down regulation of ETB receptors. Thus, Kikuchi does not render the present invention obvious.

Furthermore, Kikuchi provides no suggestion that antagonizing the ETB receptor would prevent the development of a melanoma from a melanocyte. The experiments in Kikuchi are not concerned with the treatment of melanoma, but rather with comparing the expression of ET receptors between primary melanoma cell line and metastatic melanoma cell lines, and studying the mitogenic effects of ET on various melanoma cell lines (Kikuchi at page 734). From Kikuchi, no conclusion could be drawn regarding the effect of BQ-788 on metastatic melanoma cells, or melanocytes. Thus, the difference between the subject matter of the present invention and the teachings in Kikuchi are so great that the subject matter as a whole is not obvious at the time the invention was made to one skilled in the art. There is no reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does. Any allegation that Kikuchi rendered the present invention obvious must be from hindsight, which should be avoided.

In view of the foregoing, Applicants submit that the teachings of Kikuchi do not make obvious the methods of the claimed invention. Therefore, Applicants respectfully request that the rejection of claims 43-46, 48, 50, 53, and 56-59 under 35 U.S.C. § 103(a) for being obvious over Kikuchi be withdrawn.

2. **The Pending Claims Are Not Obvious over Kikuchi in view of Battistini**

Claims 43-46, 48, 50-59 are rejected under 35 U.S.C. § 103(a) as obvious over Kikuchi in view of Battistini *et al.*, 1998, Pulmonary Pharmacology and Therapeutics. 11:97-112 ("Battistini").

Battistini discusses the use of several selective ET receptor antagonists, such as IRL-1038, RES-701-1 and BQ-788, in order to inhibit the effects induced by ETs. The Examiner alleges that it would have been prima facie obvious at the time the claimed invention was made to substitute IRL-1038 or RES-701 for the BQ-788 taught by Kikuchi.

As discussed above, the teachings of Kikuchi do not make obvious the methods of the invention for preventing development of a melanocyte to a primary melanoma and/or treatment of metastatic melanoma. Since the teachings of Kikuchi do not suggest the desirability of administering BQ-788 to selectively antagonize the ETB receptor for the methods of the present invention, there would certainly be no motivation for one skilled in the art to substitute IRL-1038 or RES-701 for the BQ-788 taught by Kikuchi.

Furthermore, Battistini does not cure the deficiencies of Kikuchi. Battistini neither teaches nor suggests methods of the present invention comprising administering a therapeutically effective amount of a selective endothelin B receptor antagonist, including ETB IRL-1038, RES-701-1 or BQ-788, to a patient in need thereof. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974), *M.P.E.P.* 2143.03. Neither Kikuchi nor Battistini by themselves or combined disclose each and every limitation of the claimed invention, and thus, the rejection cannot stand.

Applicants respectfully request that the rejection of claims 43-46, 48, 50-59 under 35 U.S.C. § 103(a) for being obvious over Kikuchi in view of Battistini be withdrawn.

3. **The Pending Claims Are Not Obvious over Kilkuchi in view of Ferrara**

Claims 43-50, 53, and 56-59 are rejected under 35 U.S.C. § 103(a) as obvious over Kikuchi in view of in view of U.S. Patent No. 5,573,762 to Ferrara *et al.* ("Ferrara").

Ferrara teaches the use of endothelin antagonists, including antibodies and inhibitory peptides, for the treatment of cardiac hypertrophy. The Examiner alleged that it would have been prima facie obvious at the time the invention was made to substitute an anti-endothelin B antagonistic antibody, as taught in Ferrara, for the BQ-788 taught by Kikuchi.

As discussed above, the teachings of Kikuchi do not make obvious the methods of the invention for preventing development of a melanocyte to a primary melanoma and/or treatment of metastatic melanoma. Since the teachings of Kikuchi do not suggest the desirability of administering BQ-788 to selectively antagonize the ETB receptor for the methods of the present invention, there would certainly be no motivation for one skilled in the art to substitute an anti-endothelin B antagonistic antibody for the BQ-788 taught by Kikuchi.

Furthermore, Ferrara does not cure the deficiencies of Kikuchi. Ferrara neither teaches nor suggests methods of the present invention comprising administering a therapeutically effective amount of a selective endothelin B receptor antagonist, including an anti-endothelin B antagonistic antibody, to a patient in need thereof. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974), *M.P.E.P.* 2143.03. Neither Kikuchi nor Ferrara by themselves or combined disclose each and every limitation of the claimed invention, and thus, the rejection cannot stand.

Applicants respectfully request that the rejection of claims 43-50, 53, and 56-59 under 35 U.S.C. § 103(a) for being obvious over Kikuchi in view of Ferrara be withdrawn.

**CONCLUSION**

Applicants respectfully request that the amendments and remarks made herein be entered and made of record in the file history of the present application. Withdrawal of the rejections in the previous Office Action and a notice of allowance are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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